



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,446	02/23/2004	Lauren Otsuki	NOCAR.007A	1443
210 7590 06/25/2009 MERCK AND CO., INC P O BOX 2000 RAHWAY, NJ 07065-0907				
EXAMINER				
ROYDS, LESLIE A				
ART UNIT		PAPER NUMBER		
1614				
MAIL DATE		DELIVERY MODE		
06/25/2009		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/785,446

Applicant(s)

OTSUKI ET AL.

Examiner

LESLIE A. ROYDS

Art Unit

1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 1-9 and 14-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-13 and 26-34 is/are rejected.
- 7) ☒ Claim(s) 30 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 27Sept04; 14Oct04; 23Oct06; 21Nov07; 20Jun08; 24July08
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1-34 are presented for examination.

Acknowledgement is made of Applicant's claim for benefit under 35 U.S.C. 119(e) to U.S. Provisional Patent Application Nos. 60/449,953, filed February 24, 2003; 60/464,812, filed April 21, 2003; 60/450,499, filed February 25, 2003; 60/464,815, filed April 21, 2003; 60/451,326, filed February 28, 2003; 60/464,811, filed April 21, 2003; 60/450,500, filed February 25, 2003; and 60/464,813, filed April 21, 2003.

Applicant's Information Disclosure Statements (IDS) filed September 27, 2004 (four pages); October 14, 2004 (one page); October 23, 2006 (one page); November 21, 2007 (one page); June 20, 2008 (one page); and July 24, 2008 (two pages), have each been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08 (10 pages total), the Examiner has considered the cited references.

Requirement for Restriction/Election

Applicant's election of the invention of Group II (claims 10-13 and 26-34), directed to a method for treating a cardiovascular disease comprising the administration of a pharmaceutical composition comprising an adenosine A₁ receptor antagonist (AA₁RA) and a beta-blocker, and the elections of (a) heart failure as the single disclosed specie of cardiovascular disease, (b) the compound KW-3902 as the single disclosed specie of AA₁RA compound [where KW-3902 is a species of Formula (I) wherein



$R_1=CH_3CH_2CH_2$, $R_2=CH_3CH_2CH_2$, $R_3=H$, $X_1=O$, $X_2=O$ and $Q=$ (wherein as in instant claim 30, Y is a single bond and $n=0$) and is also known as 8-(3-noradamantyl)-1,3-dipropylxanthine at p.3, para.[0009] of the instant specification], and (c) acebutolol as the single disclosed specie of beta-blocker, in the reply filed February 17, 2009 is acknowledged by the Examiner. Because Applicant did

Art Unit: 1614

not distinctly and specifically point out the supposed errors in the requirement, the election has been treated as an election without traverse (MPEP §818.03(a)).

Therefore, for the reasons above and those made of record at pages 2-15 of the previous Office Action dated February 11, 2008, the requirement remains proper and is hereby made **FINAL**.

Claims 1-9 and 14-25 are withdrawn from examination pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

The claims corresponding to the elected subject matter are claims 10-13 and 26-34 and such claims are herein acted on the merits.

Objection to the Abstract

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because of the repeated use of the phrase "Disclosed are..." in lines 1 and 4 of the abstract, which should be avoided. Correction is required. See MPEP § 608.01(b).

Objection to the Claims

Claim 30 is objected to for reciting the acronym "said AAIRA" without defining it previously in the claims. Correction is required. For the purposes of examination, it is understood that the term "AAIRA" is defined in the instant specification as an "adenosine A1 receptor antagonist". This is supported by the instant specification at, e.g., p.2, para.[0003].

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claim 32 is directed to the method of claim 26, wherein the AA1RA is KW-3902 or a pharmaceutically acceptable salt, ester, amide or metabolite thereof. Present claim 33 is also directed to the method of claim 26, wherein the beta-blocker is acebutolol or a pharmaceutically acceptable salt, prodrug, ester or amide thereof.

In particular, the specification and claims as originally filed fail to provide adequate written support for the instantly claimed genus of (1) pharmaceutically acceptable esters, amides or metabolites of KW-3902 (claim 32) or (2) pharmaceutically acceptable prodrugs, esters or amides of acebutolol (claim 33).

Regarding the requirement for adequate written description, Applicant's attention is directed to the MPEP at §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description

Art Unit: 1614

requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant discloses at p.7-8, para.[0025], of the instant specification, "Thus, in one aspect, the present disclosure relates to a pharmaceutical composition comprising a beta-blocker and an adenosine A1 receptor antagonist (AA1RA). The beta-blocker may be selected from the group consisting of acebutolol hydrochloride, atenolol, betaxolol hydrochloride, bisoprolol fumarate, carteolol hydrochloride, esmolol hydrochloride, metoprolol, metoprolol tartrate, nadolol, penbutolol sulfate, pindolol, propranolol hydrochloride, succinate, and timolol maleate, or a pharmaceutically acceptable salt, prodrug, ester, or amide thereof."

Regarding the instantly claimed genus of pharmaceutically acceptable esters or amides of the AA1RA compound KW-3902 or pharmaceutically acceptable esters or amides of the beta-blocker compound acebutolol (claims 32-33), Applicant has failed to provide sufficient written description to support the use of pharmaceutically acceptable esters or amides of KW-3902 and/or acebutolol. Though Applicant generally references the genus of "pharmaceutically acceptable esters or amides" of each of KW-3902 and acebutolol, the present disclosure fails to recite any structural characteristics, chemical formula, name(s) or physical characteristics of the pharmaceutically acceptable esters or amides of KW-3902 or the pharmaceutically acceptable esters or amides of acebutolol such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the genus of "pharmaceutically acceptable esters or amides" of KW3902 and/or acebutolol and, thus, would have

Art Unit: 1614

been apprised of the metes and bounds of the instantly claimed genera. Additionally, there is no direction as to what degree of derivation a compound may have from the parent KW-3902 and/or acebutolol compound and still be considered a "pharmaceutically acceptable ester" or a "pharmaceutically acceptable amide" (and still preserve substantially equivalent therapeutic efficacy for the condition(s) to be treated in the claims as KW-3902 *per se* or acebutolol *per se*) as intended by Applicant.

While it may be construed that the fact that the ester or amide is based upon the parent KW-3902 or acebutolol structure implies some sort of chemical or structural characteristics sufficient to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, it is herein noted that Applicant has failed to describe in any certain terms the degree of derivation or similarity that a compound may have from KW-3902 and/or acebutolol and still be considered an ester or amide for use in the invention as presently claimed with the expectation of the same (or at least substantially equivalent) therapeutic efficacy. The mere fact that the only chemical or structural characteristics of the compound is that it is an ester or amide of KW-3902 or acebutolol, wherein the degree of similarity or derivation from KW-3902 *per se* or acebutolol *per se* is herein undefined in the accompanying specification, is not sufficient to provide an adequate description of the genus of compounds intended by Applicant for use in the present invention. In the absence of such description, Applicant's limitation directed to "pharmaceutically acceptable esters" or "pharmaceutically acceptable amides" of either KW-3902 or acebutolol is not sufficiently supported by the present disclosure in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Regarding the instantly claimed genus of pharmaceutically acceptable metabolites of KW-3902 (claim 32), Applicant has failed to provide sufficient written description to support the use of pharmaceutically acceptable KW-3902 metabolites. In fact, the present disclosure fails to recite any structural characteristics, chemical formula, name(s) or physical characteristics, let alone any exemplary species, which would provide adequate written description of the metabolites of KW-3902 that Applicant

was actually in possession of, and intended to be used within the context of the present invention, at the time of the present invention. The specification fails to contain any exemplary compounds, limiting definition or any structural, chemical or physical characteristics of these metabolite forms such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds and still be considered a "metabolite" as intended by Applicant.

While it may be construed that the fact that the compound is based upon, or derived from, the parent KW-3902 structure implies some sort of chemical or structural characteristics sufficient to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, it is herein noted that Applicant has failed to describe in any certain terms the degree of derivation or similarity that a compound may have from KW-3902 *per se* and still be considered a metabolite for use in the invention as presently claimed. The mere fact that the only chemical or structural characteristic of the compound is that it is a metabolite of KW-3902, wherein the degree of metabolization, steps necessary to metabolize to the active agent, similarity or derivation from KW-3902 is herein undefined in the accompanying specification, is not sufficient to provide an adequate description of the genus of compounds intended by Applicant for use in the present invention. In the absence of such description, Applicant's limitation directed to metabolite forms of KW-3902 is not sufficiently supported by the present disclosure in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Lastly, regarding the instantly claimed genus of pharmaceutically acceptable prodrugs of acebutolol (claim 33), Applicant has failed to provide sufficient written description to support the use of a "prodrug" of the beta-blocker compound acebutolol. In fact, the present disclosure fails to recite any structural characteristics, chemical formula, name(s) or physical characteristics such that (1) one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the term "prodrug" and (2) the instant specification would have provided adequate written description of the prodrugs that Applicant was actually in possession of, and intended to be used

within the context of the present invention, at the time of the present invention. Though the disclosure provided above at p.7-8, para.[0025] has been noted (i.e., where Applicant generally references the genus of "prodrugs" of the disclosed beta-blocker compounds), such teachings fail to provide a clear teaching of what prodrug compounds would be considered within the scope of the term "prodrug" such that one of skill in the art would have been able to readily identify the metes and bounds of the claimed genus.

Again, while it may be construed that the mere fact that the compound is derived from or bears some correlation to the instantly claimed beta-blocker compound acebutolol by a series of conversion/transformation steps implies some sort of chemical or structural characteristic sufficient to fulfill the written description of 35 U.S.C. 112, first paragraph, it is herein noted that Applicant has failed to describe in any certain terms the degree of derivation, correlation or similarity that a compound may have from the parent compound and still be considered a prodrug that is capable of achieving the claimed therapeutic objective(s) as intended by Applicant. Applicant has also failed to tie this functional property of the disclosed prodrug of being capable of conversion to the active beta-blocking agent acebutolol in the body to some sort of chemical or physical structure. The mere fact that the only chemical or structural characteristic of the compound is that it is a prodrug of the instantly claimed acebutolol compound, wherein the degree of similarity or derivation from the parent compound is herein undefined in the accompanying specification, is not sufficient to provide an adequate description of the genus of prodrug compounds intended by Applicant for use in the present invention. In the absence of such description, Applicant's limitation to prodrugs of the claimed beta-blocker acebutolol is not sufficiently supported by the present disclosure in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed

Art Unit: 1614

invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the concept of the instantly claimed genera of (1) pharmaceutically acceptable esters, amides or metabolites of KW-3902 (claim 32) or (2) pharmaceutically acceptable prodrugs, esters or amides of acebutolol (claim 33).

Accordingly, for these reasons, the claims are properly rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-11, 13, 26-27 and 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hropot (EP 0970696 A1; 2000) in view of Alexander et al. (U.S. Patent Application Publication No. 2002/0123485; 2002), citing to STN Registry No. 34381-68-5 for evidence.

Hropot teaches a pharmaceutical composition containing a loop diuretic (i.e., additional diuretic therapy as required in Applicant's instant claims 13 and 29) and an adenosine A1-receptor antagonist and

Art Unit: 1614

the use of said combination for the simultaneous, separate or sequential administration for treating, *inter alia*, patients with congestive heart failure (p.2, para.[0006]), wherein Hropot discloses that the most preferred adenosine A1-receptor antagonist is the compound KW-3902 or a physiologically tolerable salt thereof (p.1-2, para.[0008]). Hropot further teaches that the most preferred combination of the invention is KW-3902 or a physiologically tolerable salt thereof with furosemide (i.e., the diuretic compound) or a physiologically tolerable salt thereof (p.2, para.[0011]). Note that the teaching of the treatment of a patient suffering from congestive heart failure as disclosed by Hropot is considered to necessarily meet Applicant's required limitation directed to the identification of a patient suffering from cardiovascular disease (i.e., in the instant case, specifically congestive heart failure) because the recognition of the patient as suffering from the disease is considered to be an "identification" of said patient.

Hropot fails to teach the concomitant administration of the beta blocker compound acebutolol (claim 26) or acebutolol hydrochloride (claim 33) for the treatment of congestive heart failure.

Alexander et al. teaches a combination therapy comprising an effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of a beta-adrenergic antagonist that is useful for the treatment of circulatory disorders, including, *inter alia*, congestive heart failure (p.2, para.[0011]), wherein Alexander et al. teaches that the beta-adrenergic antagonist is selected from, *inter alia*, acebutolol (p.7, para.[0060]). Alexander et al. further teaches that acebutolol may be either CAS Reg. No. 37517-30-9 or 34381-68-5 as disclosed at Table 2, which, as evidenced by STN Registry No. 34381-68-5, the acebutolol compound associated with 34381-68-5 is acebutolol hydrochloride (as recited in Applicant's instant claim 33).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the pharmaceutical composition of a diuretic and an adenosine A1-receptor antagonist (i.e., wherein KW-3902 is specifically named) useful for treating congestive heart failure as disclosed by Hropot with the pharmaceutical composition comprising a beta-adrenergic antagonist (i.e.,

Art Unit: 1614

wherein acebutolol and acebutolol hydrochloride are each specifically named), also useful for the treatment of congestive heart failure, because each pharmaceutical composition is known to have the same therapeutic use (i.e., for the treatment of congestive heart failure). Motivation to administer the compositions together as a single formulation (for simultaneous, sequential or separate use as disclosed by Hropot) flows logically from the very fact that each discrete combination of agents was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two combinations, when combined, would have, at minimum, additive, if not synergistic, effects in treating congestive heart failure when combined.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): “It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960).”

Claims 10-13 and 26-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hropot (EP 0970696 A1; 2000) in view of Alexander et al. (U.S. Patent Application Publication No. 2002/0123485; 2002), citing to STN Registry No. 34381-68-5 for evidence, as applied above to claims 10-11, 13, 26-27 and 29-34, and further in view of Fennell (“Afterload Reduction in the Therapy of Heart Failure”, *Tex Heart Inst J*, 1982 March; 9(1):61-69).

Hropot in view of Alexander et al., citing to STN Registry No. 34381-68-5 for evidence, as applied above to claims 10-11, 13, 26-27 and 29-34.

Hropot in view of Alexander et al., citing to STN Registry No. 34381-68-5 for evidence, fail to teach that the patient is also in need of after-load reduction (claims 12 and 28).

Fennell et al. teaches that in the intact heart, stroke volume (i.e., the volume of blood pumped from a ventricle per heartbeat) is reduced by an increased load and the load imposed on isolated heart muscle or the intact ventricle is referred to as the afterload (col.2, para.1, p.61). Fennell et al. discloses that heart failure is due to pulmonary vascular congestion (which results from excessive back pressure caused by inadequate emptying of the left ventricle) or to inadequate forward cardiac output (col.1-2, p.62). Fennell et al. states that afterload reduction represents an attempt to lower the systemic vascular resistance without producing a fall in the blood pressure or a reflex tachycardia, such that the reduction in resistance is converted into an increase in stroke volume (col.1, para.2, p.62). Fennell et al. teaches various methods of afterload reduction at p.63-65.

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious that the congestive heart failure patient to be treated via the teachings of Hropot in view of Alexander et al. would have also been one in need of afterload reduction because, as evidenced by Fennell et al., patients with congestive heart failure experience inadequacy of the heart in emptying the ventricle of its blood volume, which results in an increased afterload by increasing vascular resistance (i.e., reducing contractility of the heart) and requiring the heart to generate an increased amount of pressure in order to effectively eject blood from the ventricles. The skilled artisan would have reasonably expected that the congestive heart failure patient to be treated via the teachings of Hropot in view of Alexander et al. would have also benefited from afterload reduction in order to reduce vascular resistance caused by the increased afterload that results in congestive heart failure so as to increase the stroke volume of the heart to effect more complete emptying of the ventricles and better cardiac output, efficiency and contractility of the heart muscle.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is

Art Unit: 1614

appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-13 and 26-34 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 54-67 and 74-76 of U.S. Patent Application No. 10/830,617; or claims 21-34 of U.S. Patent Application No. 11/248,479; or claims 1-26 of U.S. Patent Application No. 11/248,905; or claims 1-5 and 8-14 of U.S. Patent Application No. 11/454,665; or claims 1-31 and 37-41 of U.S. Patent Application No. 12/058,129, each alternatively in view of Hropot (EP 0970696 A1; 2000), Alexander et al. (U.S. Patent Application Publication No. 2002/0123485; 2002), citing to STN Registry No. 34381-68-5 for evidence, and further in view of Fennell ("Afterload Reduction in the Therapy of Heart Failure", *Tex Heart Inst J*, 1982 March; 9(1):61-69).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending applications are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims of the '617 application clearly provide for the identification of a human patient suffering from congestive heart failure and renal impairment and intravenously administering to the patient KW-3902 or a pharmaceutically acceptable salt, ester, amide, metabolite or prodrug thereof, in conjunction with a non-adenosine modifying diuretic, such as, *inter alia*, a proximal diuretic, a loop

Art Unit: 1614

diuretic (i.e., furosemide, as in copending claims 74-76), or a distal diuretic, for the improvement or restoration of renal function.

The copending claims of the '479 application are directed to the treatment of a subject suffering from congestive heart failure comprising administering to the subject an amount of KW-3902 or a pharmaceutically acceptable salt, ester, amide, prodrug or metabolite thereof, and a therapeutically effective amount of diuretic, such as a proximal diuretic, loop diuretic or distal diuretic, such as furosemide. The copending claims also provide for the subject to be refractory to standard diuretic therapy.

The copending claims of the '905 application are directed to the treatment of a subject suffering from congestive heart failure comprising administering to the subject an amount of KW-3902 or a pharmaceutically acceptable salt, ester, amide, metabolite or prodrug thereof, in conjunction with a diuretic, such as a proximal, loop or distal diuretic, such as furosemide. The copending claims also provide for the improvement, maintenance or restoration of renal function using the same combination.

The copending claims of the '665 application are directed to the treatment of a human subject with impaired renal function that suffers from congestive heart failure comprising administering to said subject a pharmaceutical composition comprising an effective amount of KW-3902 or a pharmaceutically acceptable salt, ester or amide thereof and a therapeutically effective amount of a non-adenosine modifying diuretic, such as a proximal, loop or distal diuretic, such as furosemide, wherein the KW-3902 and the diuretic are administered substantially simultaneously or sequentially and further wherein the subject is or is not refractory to standard diuretic therapy.

The copending claims of the '129 application are directed to a method of identifying and treating an individual suffering from congestive heart failure and in need of improved, maintained or restored renal function comprising administering to said individual a therapeutically effective amount of KW-3902 or a pharmaceutically acceptable salt, amide, prodrug, ester or metabolite thereof, and a non-adenosine

Art Unit: 1614

modifying diuretic, such as a proximal, loop or distal diuretic, such as furosemide, and further provide for wherein the patient is refractory to standard diuretic therapy. The copending claims are also directed to the treatment of an individual with both congestive heart failure and mild to severe renal impairment comprising administering the same combination of agents, and further provide for wherein the patient is refractory to standard diuretic therapy. Still further, the copending claims provide for a method of maintaining or improving renal function in an individual with stable congestive heart failure who is also receiving chronic diuretic therapy comprising administering a therapeutically effective amount of an adenosine A1 receptor antagonist (AA1RA), such as KW-3902 (copending claim 38)

The copending claims fail to teach the treatment of congestive heart failure *per se* (instant claims 10 and 26), the administration of the beta-blocking compound acebutolol or acebutolol hydrochloride (instant claims 10, 26 and 33), that the patient is in need of afterload reduction (claims 12 or 28) or that the KW-3902 and beta-blocker are administered substantially simultaneously (claim 34).

Hropot teaches a pharmaceutical composition containing a loop diuretic (i.e., additional diuretic therapy as required in Applicant's instant claims 13 and 29) and an adenosine A1-receptor antagonist and the use of said combination for the simultaneous, separate or sequential administration for treating, *inter alia*, patients with congestive heart failure (p.2, para.[0006]), wherein Hropot discloses that the most preferred adenosine A1-receptor antagonist is the compound KW-3902 or a physiologically tolerable salt thereof (p.1-2, para.[0008]).

Alexander et al. teaches a combination therapy comprising an effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of a beta-adrenergic antagonist that is useful for the treatment of circulatory disorders, including, *inter alia*, congestive heart failure (p.2, para.[0011]), wherein Alexander et al. teaches that the beta-adrenergic antagonist is selected from, *inter alia*, acebutolol (p.7, para.[0060]). Alexander et al. further teaches that acebutolol may be either CAS Reg. No. 37517-30-9 or 34381-68-5 as disclosed at Table 2, which, as evidenced by STN

Art Unit: 1614

Registry No. 34381-68-5, the acebutolol compound associated with 34381-68-5 is acebutolol hydrochloride (as recited in Applicant's instant claim 33).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the copending combination of a diuretic with KW-3902 (useful for also effecting the treatment of congestive heart failure as disclosed by Hropot) with the pharmaceutical composition comprising a beta-adrenergic antagonist (i.e., wherein acebutolol and acebutolol hydrochloride are each specifically named) as disclosed by Alexander et al., also useful for the treatment of congestive heart failure, because each pharmaceutical composition is known to have the same therapeutic use (i.e., for the treatment of congestive heart failure). Motivation to administer the compositions together as a single formulation (for simultaneous, sequential or separate use as disclosed by Hropot) flows logically from the very fact that each discrete combination of agents was known to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two combinations, when combined, would have, at minimum, additive, if not synergistic, effects in treating congestive heart failure when combined. See *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980).

Fennell et al. teaches that in the intact heart, stroke volume (i.e., the volume of blood pumped from a ventricle per heartbeat) is reduced by an increased load and the load imposed on isolated heart muscle or the intact ventricle is referred to as the afterload (col.2, para.1, p.61). Fennell et al. discloses that heart failure is due to pulmonary vascular congestion (which results from excessive back pressure caused by inadequate emptying of the left ventricle) or to inadequate forward cardiac output (col.1-2, p.62). Fennell et al. states that afterload reduction represents an attempt to lower the systemic vascular resistance without producing a fall in the blood pressure or a reflex tachycardia, such that the reduction in resistance is converted into an increase in stroke volume (col.1, para.2, p.62). Fennell et al. teaches various methods of afterload reduction at p.63-65.

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious that the congestive heart failure patient to be treated via the copending claims would have also been one in need of afterload reduction because, as evidenced by Fennell et al., patients with congestive heart failure experience inadequacy of the heart in emptying the ventricle of its blood volume, which results in an increased afterload by increasing vascular resistance (i.e., reducing contractility of the heart) and requiring the heart to generate an increased amount of pressure in order to effectively eject blood from the ventricles of the heart. The skilled artisan would have reasonably expected that the congestive heart failure patient to be treated via the copending claims in view of the teachings of Hropot and Alexander et al. would have also benefited from afterload reduction in order to reduce vascular resistance caused by the increased afterload that results in congestive heart failure so as to increase the stroke volume of the heart to effect more complete emptying of the ventricles and better cardiac output, efficiency and contractility of the heart muscle.

Accordingly, rejection of claims 10-13 and 26-34 is proper over claims 54-67 and 74-76 of U.S. Patent Application No. 10/830,617; or claims 21-34 of U.S. Patent Application No. 11/248,479; or claims 1-26 of U.S. Patent Application No. 11/248,905; or claims 1-5 and 8-14 of U.S. Patent Application No. 11/454,665; or claims 1-31 and 37-41 of U.S. Patent Application No. 12/058,129, as claiming obvious and unpatentable variants thereof. These are each provisional rejections since the claims have not, in fact, yet been patented.

Claims 10-13 and 26-34 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent Application No. 11/763,993 in view of Hropot (EP 0970696 A1; 2000), Alexander et al. (U.S. Patent Application Publication No. 2002/0123485; 2002), citing to STN Registry No. 34381-68-5 for evidence, and further in view of Fennell ("Afterload Reduction in the Therapy of Heart Failure", *Tex Heart Inst J*, 1982 March; 9(1):61-

Art Unit: 1614

69).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending applications are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims provide for a method for treating a patient for acute fluid overload, wherein the patient has congestive heart failure (copending claim 6), comprising identifying the patient in need of short-term hospitalization to treat acute fluid overload, hospitalizing the patient, administering non-adenosine modifying diuretic therapy to the patient in combination with an amount of KW-3902 or a pharmaceutically acceptable salt, ester, amide, metabolite or prodrug thereof, wherein the diuretic may be, *inter alia*, furosemide, etc. (copending claims 4-5) and further wherein a beta-blocker may be administered also (copending claim 20). The copending claims further provide for a method of reducing the treatment time to achieve adequate diuresis in a patient experiencing acute fluid overload or congestive heart failure, comprising administering a therapeutically effective amount of KW-3902 or a pharmaceutically acceptable salt, ester, amide, metabolite or prodrug thereof and a non-adenosine modifying diuretic therapy, such as, *inter alia*, furosemide, and further wherein a beta-blocker may also be administered (copending claim 21).

The copending claims fail to teach the treatment of congestive heart failure *per se* (instant claims 10 and 26), the administration of the specific beta-blocking compound acebutolol or acebutolol hydrochloride (instant claims 10, 26 and 33), that the patient is in need of afterload reduction (claims 12 or 28) or that the KW-3902 and beta-blocker are administered substantially simultaneously (claim 34).

Hropot teaches a pharmaceutical composition containing a loop diuretic (i.e., additional diuretic therapy as required in Applicant's instant claims 13 and 29) and an adenosine A1-receptor antagonist and the use of said combination for the simultaneous, separate or sequential administration for treating, *inter alia*, patients with congestive heart failure (p.2, para.[0006]), wherein Hropot discloses that the most preferred adenosine A1-receptor antagonist is the compound KW-3902 or a physiologically tolerable salt thereof (p.1-2, para.[0008]).

Alexander et al. teaches a combination therapy comprising an effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of a beta-adrenergic antagonist that is useful for the treatment of circulatory disorders, including, *inter alia*, congestive heart failure (p.2, para.[0011]), wherein Alexander et al. teaches that the beta-adrenergic antagonist is selected from, *inter alia*, acebutolol (p.7, para.[0060]). Alexander et al. further teaches that acebutolol may be either CAS Reg. No. 37517-30-9 or 34381-68-5 as disclosed at Table 2, which, as evidenced by STN Registry No. 34381-68-5, the acebutolol compound associated with 34381-68-5 is acebutolol hydrochloride (as recited in Applicant's instant claim 33).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the compending combination of a diuretic with KW-3902 (useful for treating congestive heart failure as disclosed by Hropot) with the pharmaceutical composition comprising a beta-adrenergic antagonist (i.e., wherein acebutolol and acebutolol hydrochloride are each specifically named) as disclosed by Alexander et al., also useful for the treatment of congestive heart failure, because each pharmaceutical composition is known to have the same therapeutic use (i.e., for the treatment of congestive heart failure). Motivation to administer the compositions together as a single formulation (for simultaneous, sequential or separate use as disclosed by Hropot) flows logically from the very fact that each discrete combination of agents was known to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two combinations, when combined, would have, at minimum,

Art Unit: 1614

additive, if not synergistic, effects in treating congestive heart failure when combined and, also, that the copending claims clearly contemplated the combination of the disclosed therapy with a “beta-blocker” *per se*. See *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980).

Fennell et al. teaches that in the intact heart, stroke volume (i.e., the volume of blood pumped from a ventricle per heartbeat) is reduced by an increased load and the load imposed on isolated heart muscle or the intact ventricle is referred to as the afterload (col.2, para.1, p.61). Fennell et al. discloses that heart failure is due to pulmonary vascular congestion (which results from excessive back pressure caused by inadequate emptying of the left ventricle) or to inadequate forward cardiac output (col.1-2, p.62). Fennell et al. states that afterload reduction represents an attempt to lower the systemic vascular resistance without producing a fall in the blood pressure or a reflex tachycardia, such that the reduction in resistance is converted into an increase in stroke volume (col.1, para.2, p.62). Fennell et al. teaches various methods of afterload reduction at p.63-65.

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious that the congestive heart failure patient to be treated via the copending claims would have also been one in need of afterload reduction because, as evidenced by Fennell et al., patients with congestive heart failure experience inadequacy of the heart in emptying the ventricle of its blood volume, which results in an increased afterload by increasing vascular resistance (i.e., reducing contractility of the heart) and requiring the heart to generate an increased amount of pressure in order to effectively eject blood from the ventricles of the heart. The skilled artisan would have reasonably expected that the congestive heart failure patient to be treated via the copending claims in view of the teachings of Hropot and Alexander et al. would have also benefited from afterload reduction in order to reduce vascular resistance caused by the increased afterload that results in congestive heart failure so as to increase the stroke volume of the heart to effect more complete emptying of the ventricles and better cardiac output, efficiency and contractility of the heart muscle.

Accordingly, rejection of claims 10-13 and 26-34 is proper over claims 1-23 of U.S. Patent Application No. 11/763,993, as claiming obvious and unpatentable variants thereof. This is a provisional rejection since the claims have not, in fact, yet been patented.

Claims 10-13 and 26-34 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 and 27-36 of U.S. Patent Application No. 11/764,018; or claims 29-53 of U.S. Patent Application No. 12/058,532, each alternatively in view of Hropot (EP 0970696 A1; 2000), Alexander et al. (U.S. Patent Application Publication No. 2002/0123485; 2002), citing to STN Registry No. 34381-68-5 for evidence, and further in view of Fennell ("Afterload Reduction in the Therapy of Heart Failure", *Tex Heart Inst J*, 1982 March; 9(1):61-69).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending applications are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims of the '018 application clearly provide for methods of treating a patient suffering from congestive heart failure, comprising providing or administering a therapeutically effective amount of an AA1RA compound, such as, *inter alia*, KW-3902, or a pharmaceutically acceptable salt, ester, amide, prodrug or metabolite thereof (copending claim 7). The copending claims also provide for a method of improving and/or maintaining renal function in individuals with stable congestive heart failure that are taking chronic diuretics, comprising administering to said individual a therapeutically effective amount of an AA1RA compound, such as, *inter alia*, KW-3902, or a pharmaceutically acceptable salt,

Art Unit: 1614

ester, amide, prodrug or metabolite thereof (copending claim 28).

The copending claims of the '532 application provide for a method of preventing or delaying the onset of renal impairment in a subject with fluid overload or congestive heart failure comprising administering a composition comprising at least 20 mg of KW-3902 or a pharmaceutically acceptable salt, ester, prodrug, amide, or metabolite thereof. The copending claims further provide for a method of treating a subject suffering from congestive heart failure comprising administering a composition comprising at least 20 mg of KW-3902 or a pharmaceutically acceptable salt, ester, prodrug, amide or metabolite thereof.

The copending claims fail to teach the administration of the specific beta-blocking compound acebutolol or acebutolol hydrochloride (instant claims 10, 26 and 33), that the patient is in need of afterload reduction (claims 12 or 28) or that the KW-3902 and beta-blocker are administered substantially simultaneously (claim 34).

Hropot teaches a pharmaceutical composition containing a loop diuretic (i.e., additional diuretic therapy as required in Applicant's instant claims 13 and 29) and an adenosine A1-receptor antagonist and the use of said combination for the simultaneous, separate or sequential administration for treating, *inter alia*, patients with congestive heart failure (p.2, para.[0006]), wherein Hropot discloses that the most preferred adenosine A1-receptor antagonist is the compound KW-3902 or a physiologically tolerable salt thereof (p.1-2, para.[0008]).

Alexander et al. teaches a combination therapy comprising an effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of a beta-adrenergic antagonist that is useful for the treatment of circulatory disorders, including, *inter alia*, congestive heart failure (p.2, para.[0011]), wherein Alexander et al. teaches that the beta-adrenergic antagonist is selected from, *inter alia*, acebutolol (p.7, para.[0060]). Alexander et al. further teaches that acebutolol may be either CAS Reg. No. 37517-30-9 or 34381-68-5 as disclosed at Table 2, which, as evidenced by STN

Art Unit: 1614

Registry No. 34381-68-5, the acebutolol compound associated with 34381-68-5 is acebutolol hydrochloride (as recited in Applicant's instant claim 33).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the copending combination of a diuretic with KW-3902 (useful for treating congestive heart failure as disclosed by Hropot) with the pharmaceutical composition comprising a beta-adrenergic antagonist (i.e., wherein acebutolol and acebutolol hydrochloride are each specifically named) as disclosed by Alexander et al., also useful for the treatment of congestive heart failure, because each pharmaceutical composition is known to have the same therapeutic use (i.e., for the treatment of congestive heart failure). Motivation to administer the compositions together as a single formulation (for simultaneous, sequential or separate use as disclosed by Hropot) flows logically from the very fact that each discrete combination of agents was known to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two combinations, when combined, would have, at minimum, additive, if not synergistic, effects in treating congestive heart failure when combined. See *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980).

Fennell et al. teaches that in the intact heart, stroke volume (i.e., the volume of blood pumped from a ventricle per heartbeat) is reduced by an increased load and the load imposed on isolated heart muscle or the intact ventricle is referred to as the afterload (col.2, para.1, p.61). Fennell et al. discloses that heart failure is due to pulmonary vascular congestion (which results from excessive back pressure caused by inadequate emptying of the left ventricle) or to inadequate forward cardiac output (col.1-2, p.62). Fennell et al. states that afterload reduction represents an attempt to lower the systemic vascular resistance without producing a fall in the blood pressure or a reflex tachycardia, such that the reduction in resistance is converted into an increase in stroke volume (col.1, para.2, p.62). Fennell et al. teaches various methods of afterload reduction at p.63-65.

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious that the congestive heart failure patient to be treated via the copending claims would have also been one in need of afterload reduction because, as evidenced by Fennell et al., patients with congestive heart failure experience inadequacy of the heart in emptying the ventricle of its blood volume, which results in an increased afterload by increasing vascular resistance (i.e., reducing contractility of the heart) and requiring the heart to generate an increased amount of pressure in order to effectively eject blood from the ventricles of the heart. The skilled artisan would have reasonably expected that the congestive heart failure patient to be treated via the copending claims in view of the teachings of Hropot and Alexander et al. would have also benefited from afterload reduction in order to reduce vascular resistance caused by the increased afterload that results in congestive heart failure so as to increase the stroke volume of the heart to effect more complete emptying of the ventricles and better cardiac output, efficiency and contractility of the heart muscle.

Accordingly, rejection of claims 10-13 and 26-34 is proper over claims 1-25 and 27-36 of U.S. Patent Application No. 11/764,018; or claims 29-53 of U.S. Patent Application No. 12/058,532, as claiming obvious and unpatentable variants thereof. This is a provisional rejection since the claims have not, in fact, yet been patented.

Claims 10-13 and 26-34 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-21 of U.S. Patent Application No. 11/107,637 in view of Alexander et al. (U.S. Patent Application Publication No. 2002/0123485; 2002), citing to STN Registry No. 34381-68-5 for evidence.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference

Art Unit: 1614

claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending applications are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims provide for a method of treating cardiovascular disease, such as congestive heart failure (copending claim 19), wherein the method comprises identifying a patient in need of such treatment and administering a pharmaceutical composition comprising an aldosterone inhibitor and an AA1RA compound simultaneously (copending claim 17), wherein the patient is also in need of afterload reduction (copending claim 20) and/or requires additional diuretic therapy or is refractory to diuretic therapy (copending claim 21). Though the copending claims do not specifically recite the AA1RA compound of the instant claims [i.e., KW-3902; also known as (8-(3-noradamantyl)-1,3-dipropylxanthine per p.3, para.[0009] of the instant specification], the copending specification defines the AA1RA compounds usable for the instant invention as, *inter alia*, 8-(noradamantan-3-yl)-1,3-dipropylxanthine (p.5, para.[0020]). Thus, the AA1RA compounds to be used in the copending method clearly circumscribe the use of the instantly claimed KW-3902 [also known as (8-(3-noradamantyl)-1,3-dipropylxanthine per p.3, para.[0009] of the instant specification] compound. Please note that, in the instant case, the disclosure of the copending patent application is being relied upon solely to define the meaning of the term “AA1RA”, which is consistent with the MPEP at §804, which states, “The specification can be used as a dictionary to learn the meaning of a term used in the patent claim. *Toro Co. v. White Consol. Indus., Inc.* 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999).”

The copending claims fail to teach the administration of the beta-blocker compound acebutolol or acebutolol hydrochloride (instant claims 10, 26 and 33).

Alexander et al. teaches a combination therapy comprising an effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of a beta-adrenergic

Art Unit: 1614

antagonist that is useful for the treatment of circulatory disorders, including, *inter alia*, congestive heart failure (p.2, para.[0011]), wherein Alexander et al. teaches that the beta-adrenergic antagonist is selected from, *inter alia*, acebutolol (p.7, para.[0060]). Alexander et al. further teaches that acebutolol may be either CAS Reg. No. 37517-30-9 or 34381-68-5 as disclosed at Table 2, which, as evidenced by STN Registry No. 34381-68-5, the acebutolol compound associated with 34381-68-5 is acebutolol hydrochloride (as recited in Applicant's instant claim 33).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the copending combination useful for treating congestive heart failure with the pharmaceutical composition comprising a beta-adrenergic antagonist (i.e., wherein acebutolol and acebutolol hydrochloride are each specifically named), also useful for the treatment of congestive heart failure, because each pharmaceutical composition is known to have the same therapeutic use (i.e., for the treatment of congestive heart failure). Motivation to administer the compositions together as a single formulation flows logically from the very fact that each discrete combination of agents was known to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two combinations, when combined, would have, at minimum, additive, if not synergistic, effects in treating congestive heart failure when combined. See *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980).

Accordingly, rejection of claims 10-13 and 26-34 is proper over claims 16-21 of U.S. Patent Application No. 11/107,637, as claiming obvious and unpatentable variants thereof.

Claims 10-13 and 26-34 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7-10, 13, 17-19 and 21 of U.S. Patent Application No. 12/485,797 in view of Alexander et al. (U.S. Patent Application Publication No. 2002/0123485; 2002), citing to STN Registry No. 34381-68-5 for evidence, and Fennell ("Afterload

Art Unit: 1614

Reduction in the Therapy of Heart Failure”, *Tex Heart Inst J*, 1982 March; 9(1):61-69).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending applications are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims provide for a method of treating cardiovascular disease, such as congestive heart failure (copending claim 19), wherein the method comprises administering an aldosterone inhibitor and an AA1RA compound simultaneously (copending claim 17), wherein the patient requires additional diuretic therapy or is refractory to diuretic therapy (copending claim 21) and the AA1RA compound may be, *inter alia*, 8-(noradamantan-3-yl)-1,3-dipropylxanthine (which is identical to Applicant’s elected compound KW-3902, which is also known as (8-(3-noradamanty1)-1,3-dipropylxanthine per p.3, para.[0009] of the instant specification, and per Applicant’s remarks filed February 17, 2009, has the same structure as that of the copending claims wherein $R_1=CH_3CH_2CH_2$, $R_2=CH_3CH_2CH_2$, $R_3=H$, $X_1=O$,



$X_2=O$ and $Q=$ (wherein as in copending claim 3, Y is a single bond and $n=0$).

The copending claims fail to teach the administration of the beta-blocker compound acebutolol or acebutolol hydrochloride (instant claims 10, 26 and 33) or that the patient is in need of after-load reduction (instant claims 12 and 28).

Alexander et al. teaches a combination therapy comprising an effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of a beta-adrenergic antagonist that is useful for the treatment of circulatory disorders, including, *inter alia*, congestive heart

Art Unit: 1614

failure (p.2, para.[0011]), wherein Alexander et al. teaches that the beta-adrenergic antagonist is selected from, *inter alia*, acebutolol (p.7, para.[0060]). Alexander et al. further teaches that acebutolol may be either CAS Reg. No. 37517-30-9 or 34381-68-5 as disclosed at Table 2, which, as evidenced by STN Registry No. 34381-68-5, the acebutolol compound associated with 34381-68-5 is acebutolol hydrochloride (as recited in Applicant's instant claim 33).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the copending combination useful for treating congestive heart failure with the pharmaceutical composition comprising a beta-adrenergic antagonist (i.e., wherein acebutolol and acebutolol hydrochloride are each specifically named) as disclosed by Alexander et al., also useful for the treatment of congestive heart failure, because each pharmaceutical composition is known to have the same therapeutic use (i.e., for the treatment of congestive heart failure). Motivation to administer the compositions together as a single formulation flows logically from the very fact that each discrete combination of agents was known to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two combinations, when combined, would have, at minimum, additive, if not synergistic, effects in treating congestive heart failure when combined. See *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980).

Fennell et al. teaches that in the intact heart, stroke volume (i.e., the volume of blood pumped from a ventricle per heartbeat) is reduced by an increased load and the load imposed on isolated heart muscle or the intact ventricle is referred to as the afterload (col.2, para.1, p.61). Fennell et al. discloses that heart failure is due to pulmonary vascular congestion (which results from excessive back pressure caused by inadequate emptying of the left ventricle) or to inadequate forward cardiac output (col.1-2, p.62). Fennell et al. states that afterload reduction represents an attempt to lower the systemic vascular resistance without producing a fall in the blood pressure or a reflex tachycardia, such that the reduction in

Art Unit: 1614

resistance is converted into an increase in stroke volume (col.1, para.2, p.62). Fennell et al. teaches various methods of afterload reduction at p.63-65.

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious that the congestive heart failure patient to be treated via the copending claims would have also been one in need of afterload reduction because, as evidenced by Fennell et al., patients with congestive heart failure experience inadequacy of the heart in emptying the ventricle of its blood volume, which results in an increased afterload by increasing vascular resistance (i.e., reducing contractility of the heart) and requiring the heart to generate an increased amount of pressure in order to effectively eject blood from the ventricles of the heart. The skilled artisan would have reasonably expected that the congestive heart failure patient to be treated via the copending claims in view of the teachings of Alexander et al. would have also benefited from afterload reduction in order to reduce vascular resistance caused by the increased afterload that results in congestive heart failure so as to increase the stroke volume of the heart to effect more complete emptying of the ventricles and better cardiac output, efficiency and contractility of the heart muscle.

Accordingly, rejection of claims 10-13 and 26-34 is proper over claims 1-5, 7-10, 13, 17-19 and 21 of U.S. Patent Application No. 12/485,797, as claiming obvious and unpatentable variants thereof.

Conclusion

Rejection of claims 10-13 and 26-34 is proper.

Claims 1-9 and 14-25 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE A. ROYDS whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

Art Unit: 1614

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

June 22, 2009